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Synthetic procedure to heteroaromatic pyrido[2,1-*f*][1,2,4]triazinium salt and related compounds

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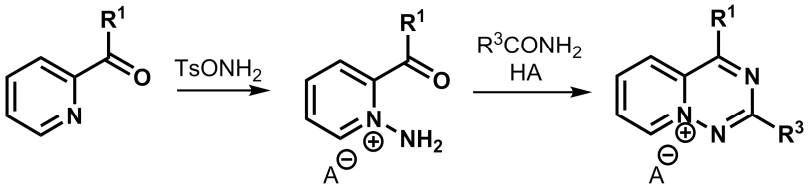
Institute of Organic Chemistry and NMR Research Laboratory of Instrumentation Centre, Research Centre for Natural Sciences, Hungarian Academy of Sciences, H-1117 Budapest, Magyar tudósok körútja 2.



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Synthetic procedure to pyrido[2,1-*f*][1,2,4]triazinium salt and related compounds

Sándor Bátori[a§], Dorottya Csányi[a], Daniella Takács[a], Orsolya Egyed[b], Zsuzsanna Riedl[a], and György Hajós[a]*

[a]Institute of Organic Chemistry and [b]NMR Research Laboratory of Instrumentation Centre, Research Centre for Natural Sciences, Hungarian Academy of Sciences, H-1117 Budapest, Magyar tudósok körútja 2.

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ABSTRACT

N-aminopyridyl ketone salts were reacted with formamide to yield heteroaromatic pyrido[2,1-*f*][1,2,4]triazinium salts. Upon storage of these products in the presence of water, formation of covalent hydrates have been observed. Reaction of the same starting compound with urethane yielded 3-chloropyrido[2,1-*f*][1,2,4]triazinium salt which readily reacted with secondary amines to afford 3-amino derivatives. An analogous ring closure reaction of 2-formylaminomethyl- and formaminobenzylpyridine allowed the synthesis of the partially reduced 3,4-dihydropyrido[2,1-*f*][1,2,4]triazinium compounds. The cyclization procedure was also applied for the synthesis of the related pyrimido[2,1-*f*][1,2,4]triazinium salt.

1. Introduction

Large number of fused [1,2,4]triazines have been published in the literature and, also, extensive reviews[1,2] appeared. Among these compounds, however, relatively few data are available on ring systems with positively charged bridge head nitrogen atom. Four structural variations of such heteroaromatic cation can exist as shown by Fig 1.

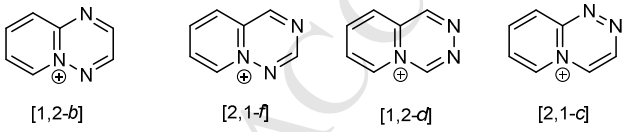


Figure 1. **The possible heteroaromatic cations of pyrido[1,2,4]triazinium bicycle with bridge-head nitrogen atom**

Out of these four cations, interestingly, synthesis of only pyrido[1,2-*b*][1,2,4]triazinium ring system[3,4,5] as well as its isoquinoline-fused analogues[6,7] has been described in details.

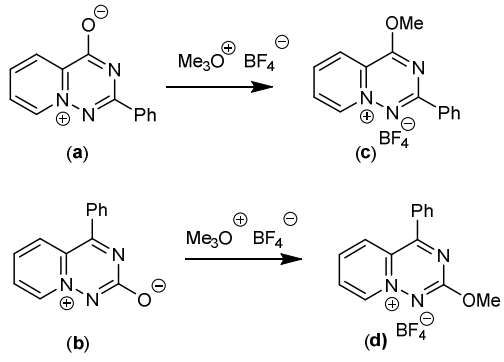


Figure 2. **Transformation of zwitterions a and b to methoxy substituted pyrido[2,1-*f*][1,2,4]triazinium salts c and d.**

On formation of the second ring system: pyrido[2,1-*f*][1,2,4]triazinium cation two pieces of literature information are available: (i) preliminary notes on its synthesis have been published without any experimental detail[8,9]; (ii) zwitterions **a**

* Corresponding author. Institute of Organic Chemistry, Research Center for Natural Sciences, Hungarian Academy of Sciences. H-1117 Budapest Budapest, Magyar tudósok körútja 2.

E-Mail address: hajos.gyorgy@ttk.mta.hu

§Present address: H-1214 Budapest, Rákóczi F. út 268/A

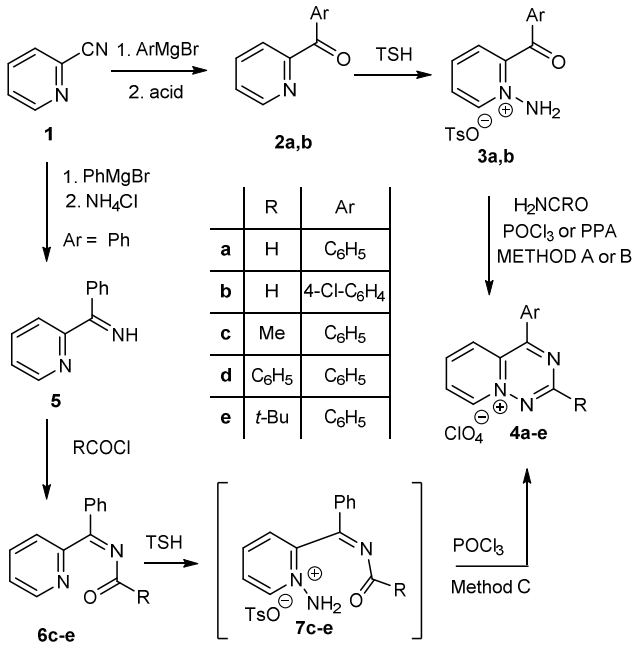
and **b** (Figure 2) have been synthesized and treated with trimethyl oxonium fluoroborate to yield 1-methoxy-3-phenylpyrido[1,2,4]triazinium fluoroborate **c** and 3-methoxy-1-phenylpyrido[1,2,4]triazinium fluoroborate **d**, respectively[10].

While more detailed descriptions on the tricyclic analogues of this ring system in patent literature have been disclosed[11] due to some valuable biological effects of these derivatives, no preparative procedure has yet been reported on the synthesis of the basic bicyclic heteroaromatic pyrido[2,1-*f*][1,2,4]triazinium salt.

Herewith we report on the detailed synthetic route to pyrido[2,1-*f*][1,2,4]triazinium salts and describe the first structure elucidation of these compounds. We also describe the synthesis of the partially reduced 3,4-dihydro derivatives as well as application of this procedure for preparation of an analogous pyrimido[2,1-*f*][1,2,4]triazinium salt.

2. Results and discussion

For the synthesis of the target ring system, two pathways have been elaborated. Common starting compound of these routes was 2-cyanopyridine (**1**) which was reacted with a Grignard reagent. Acidic work up of the reaction mixture afforded 2-benzoyl or 2-p-chlorobenzoylpyridine[12] (**2a,b**, Scheme 1). When this compound was reacted with *O*-tosyl hydroxylamine (TSH)[13], the *N*-amino salt (**3a,b**) was obtained in acceptable yield (75% and 85%, respectively). Reaction of **3a,b** with the appropriate amide and phosphorus oxychloride resulted in the ring closure to the pyrido[2,1-*f*][1,2,4]triazinium salts **4a,b**.



Scheme 1

Another synthetic possibility is work up of the reaction mixture obtained from transformation of 2-cyanopyridine (**1**) and Grignard reagent in the presence of ammonium chloride. In this case extraction with organic solvent led to isolation of ketimine **5**. This intermediate proved to be a pale yellow oil, it was not purified and was transformed immediately to acylimino derivatives (**6c-e**) by treatment with the appropriate acid chloride. *N*-amination of acylketimine **6c-e** with *O*-tosyl hydroxylamine (TSH) gave the final product triazinium salt (**4c-e**) in one manipulation step. This reaction proceeded obviously *via* formation of the *N*-amino intermediate **7** which spontaneously underwent ring closure to **4**.

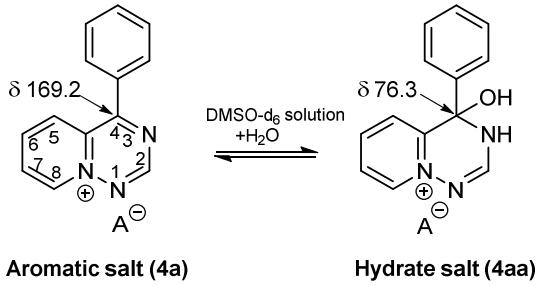
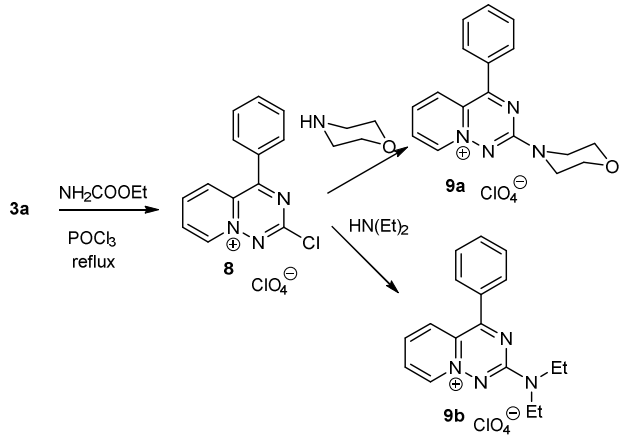


Figure 3. **Transformation of aromatic pyrido[2,1-*f*][1,2,4]-triazinium salts (4a) to covalent hydrates (4aa). The change of the chemical shift of C4 convincingly supports the fact of the water addition.**

When the DMSO solution of **4a** was allowed to stand at room temperature, its NMR spectrum underwent a gradual change: the intensity of the originally observed pattern of chemical shifts decreased and, in 3 days, a new set of signals with higher intensity appeared. As a result of this change, the ratio of the new and original component was found to be 5:1, approximately.

By comparison of this observation with results earlier found with the benzologue fused isoquinolinium salt[8] we had to assume that a covalent hydration with participation of traces of water is taking place in case of **4a** as shown in Figure 3. Thus, while the isolated **4a** exists initially in the aromatic form, reaction of this compound with water results in formation of the "hydrate salt" **4aa**. Covalent hydration of various monocyclic and fused [1,2,4]triazines was earlier known and is well documented in the literature[14,15].

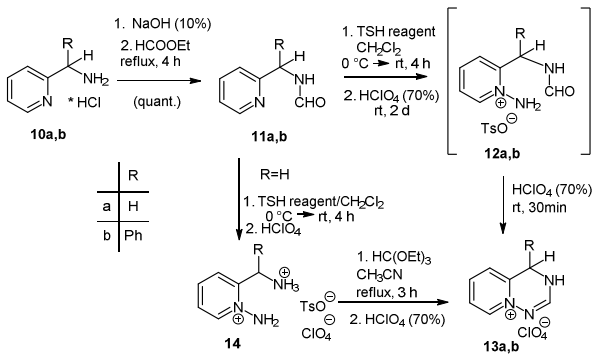
A full assignment of the two NMR spectra of these two structures has been carried out. This revealed that the structural change of the "aromatic salt" (**4a**) to "hydrate salt" (**4aa**) is convincingly supported by the change of the NMR spectra: carbon shift of C-4 appears in the aromatic species at δ 169.2, whereas this shift is to be found at essentially higher field in the hydrate salt (δ 76.3) because of the sp^3 hybrid state of this carbon atom. Similarly, an upfield change of the H-8 shift in the aromatic compound (δ 9.92) to δ 8.95 in the spectrum of the hydrate is in agreement with the decreased aromaticity of the hydrate salt. Our efforts to isolate **4aa** in pure crystalline form unfortunately failed.



Scheme 2

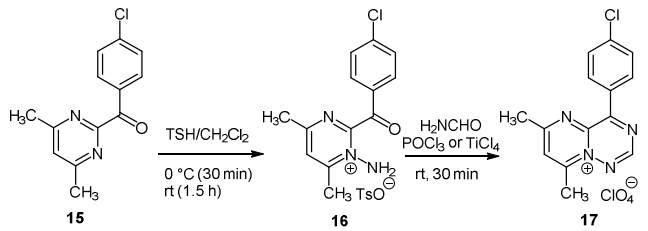
A different substitution pattern of the ring closed triazinium salt was achieved by reaction of *N*-amino ketone salt **3a** with urethane in the presence of phosphorus oxychloride. By this transformation, 2-chloropyrido[2,1-*f*][1,2,4]triazinium perchlorate (**8**) was obtained in good yield. The chlorine atom in position 2 readily underwent nucleophilic substitution with secondary amines. Thus, 2-morpholino (**9a**) and 2-diethylamino substituted salts **(9b**) were obtained with morpholine and diethylamine, respectively.

An analogous ring closure reaction to that described above can also be carried out starting from the commercially available 2-aminomethyl- (**10a**) and 2-aminobenzylpyridine (**10b**) as starting compounds. This procedure allows the synthesis of the 3,4-dihydropyrido[2,1-*f*][1,2,4]triazinium salts. Thus, formylation of **10** with ethyl formate affords the formylaminomethyl[16] (**11a**) and 2-formylaminobenzylpyridine (**11b**) which compounds upon treatment with TSH give rise to formation of the expected 3,4-dihydropyrido[2,1-*f*][1,2,4]triazinium perchlorates **13a,b**. A plausible intermediate of this last step is formation of the *N*-amino salt **12**. In case of **11a** an alternative cyclization route has also been carried out: *N*-amination and simultaneous deformylation with perchloric acid yielded the *N*-amino salt **14** which upon treatment with triethyl orthoformate gave the same ring closed **13a**.



Scheme 3

The ring closure methodology to pyrido[2,1-*f*][1,2,4]triazinium salts **4** was also successfully applied for the synthesis of the corresponding pyrimido[2,1-*f*][1,2,4]triazinium salt (Scheme 4).



Scheme 4

Thus, pyrimidyl keton **15**[17] was *N*-aminated to give the *N*-amino salt **16** which was then treated with formamide/phosphorus oxychloride. Upon addition of perchloric acid, 4-(4-chlorophenyl)-6,8-dimethylpyrimido[2,1-*f*][1,2,4]triazinium perchlorate **17** as a new ring system was obtained in modest yield.

It is important to emphasize that, in this reaction, hydrogen cyanide is evolving as side product. This can be, however, avoided by an alternative experimental method by using titanium tetrachloride instead of phosphorus oxychloride as shown in the experimental part (see Method D).

3. Conclusion

In this study, a full experimental description has been reported for the synthesis of the heteroaromatic pyrido[2,1-*f*][1,2,4]triazinium salts which was earlier disclosed only in preliminary publications. In the presence of water, formation of covalent hydrates has been observed. Similar ring closure reaction to 3,4-dihydropyrido[2,1-*f*][1,2,4]triazinium compounds has also been elaborated. The ring closure procedure was also applied for the synthesis of a related pyrimido[2,1-*f*][1,2,4]triazinium salt.

4. Experimental section

Melting points were determined on a Büchi apparatus and are uncorrected. The ID spectra were recorded on a Thermo Nicolet Avatar 320 FT-IR spectrometer. NMR experiments were carried out on Varian INOVA-300 spectrometer equipped with a 5 mm inverse detection z-gradient probe and on 500 MHz Varian NMR SYSTEM spectrometers. Measurements were performed at +30°C in $CDCl_3$ and DMSO-d_6. 1H and 13C chemical shifts are expressed in parts per million (δ) referenced to TMS or residual solvent signals. The elemental analysis has been carried out with the Elementar Vario EL III apparatus (at the Analytical Laboratory for Organic Chemistry, Institute of Organic Chemistry, Research Centre for Natural Sciences, Hungarian Academy of Sciences, Magyar tudósok körútja 2, H-1117 Budapest, Hungary). Reactions were monitored with Merck silica gel 60 F254 TLC plates (0.25 mm thickness). All chemicals and solvents were used as supplied.

*4.1. Ring Closure to Pyrido[2,1-f][1,2,4]triazinium salts (**4a-e**)*

Method A: In a well ventilating hood $POCl_3$ (6.7 g, 4 mL, 44 mmol) was dropped below 100 °C into the stirred solution of 1-amino-2-aroylpyridinium tosylate (**3a,b**, 1 mmol) in formamide (10 mL) (Caution: HCN was liberated during the process!) and stirring was continued for 30 min. The reaction mixture was poured onto crushed ice, mixed with 70% $HClO_4$ (2 mL) and extracted with nitromethane (3 x 10 mL). The organic extract was concentrated and the residue was recrystallized from a suitable solvent to give the product.

Method B: A mixture of **3a** (0.3 g, 1 mmol) with acetamide (0.6 g, 10 mmol) or benzamide (1.2 g, 10 mmol) in polyphosphoric acid (5 g) was stirred at 170 °C for 3 h. The reaction mixture was poured on ice-water, mixed with 70% $HClO_4$ (1 mL) and the precipitate was filtered off, washed with water and CCl_4 to give the product.

Method C: Into a solution of the appropriate *N*-acylketimine (**6c-e**, 10 mmol) in CH_2Cl_2 (5 mL) was dropped a freshly prepared solution of TSH (1.87 g, 10 mmol) in CH_2Cl_2 (30 mL) at room temperature. After being stirred for 1 h, the solvent was

evaporated, the residue was mixed with $POCl_3$ and refluxed for 10 min. The excess of the $POCl_3$ was evaporated in *vacuo*, the residue was poured into ice-water containing 70% $HClO_4$ (2 mL) and the precipitate was filtered off, washed with water to give the product.

*4-Phenylpyrido[2,1-f][1,2,4]triazinium perchlorate (**4a**)*

This compound was prepared by Method A to give 0.28 g (90%) of crystals, mp 259-260 °C (nitromethane-diethyl ether); [Found: C, 50.64; H, 2.97; N, 13.62; Cl, 11.52. $C_{13}H_{10}ClN_3O_4$ requires C, 50.74; H, 3.28; N, 13.66; Cl, 11.52%]; IR (KBr): 3050, 1600, 1564, 1510, 1460, 1410, 1100 cm^{-1}; UV (EtOH): 297 (4.13), 228 (4.20), shoulder: 350, 325 nm; δ_H (500 MHz, DMSO-d_6): 7.77 (2H, m, H3' + H5'), 7.84 (1H, m, H4'), 7.95 (2H, m, H2' + H6'), 8.71 (1H, ddd, *J* 7.7, 6.5, 2.1 Hz, H7), 8.86 (1H, dd, *J* 8.3, 2.1 Hz, H5), 8.91 (1H, ddd, *J* 8.3, 7.7, 1.0 Hz, H6), 9.92 (1H, dd, *J* 6.5, 1.0 Hz, H8), 9.95 (1H, s, H2); δ_C (125 MHz, DMSO-d_6): 128.3 (C5), 129.2 (C3' + C5'), 130.5 (C2' + C6'), 130.9 (C7), 132.7 (C1'), 132.8 (C4'), 135 .3 (C4a), 141.6 (C8), 144.3 (C6), 154.2 (C2), 169.2 (C4).

*Hydrate salt formation in solution: identification of 4-Hydroxy-4-phenyl-3,4-dihydropyrido[2,1-f][1,2,4]triazinium perchlorate (**4aa**)*

δ_H (500 MHz, DMSO-d_6): 7.48 (1H, m, H4'), 7.49 (2H, m, H3' + H5'), 7.55 (1H, dd, *J* 8.2, 1.2 Hz, H5), 7.66 (2H, m, H2' + H6'), 8.00 (1H, ddd, *J* 7.8, 6.7, 1.2 Hz, H7), 8.20 (1H, d, *J* 5.1 Hz, H2), 8.29 (1H, ddd, *J* 8.2, 7.8, 1.4 Hz, H6), 8.52 (1H s,,br, OH), 8.95 (1H, dd, *J* 6.7, 1.4 Hz, H8), 10.65 (1H, d, *J* 5.1 Hz, NH); δ_C (125 MHz, DMSO-d_6): 76.3 (C4), 126.8 (C5), 127.0 (C2' + C6'), 127.2 (C7), 128.6 (C3' + C5'), 129.5 (C4'), 139.6 (C8), 141.9 (C1'), 142.8 (C6), 144.3 (C4a), 146.4 (C2).

*4-(4-Chlorophenyl)pyrido[2,1-f][1,2,4]triazinium perchlorate (**4b**).*

This compound was prepared using Method A to give 0.21 g (62%) of white crystals, mp 254-255 °C (acetonitrile); [Found: C, 45.82; H, 2.71; N, 12.58. $C_{13}H_9Cl_2N_3O_4$ requires C, 45.64; H, 2.65; N, 12.78%]; IR (KBr): 3020, 1610, 1590, 1500, 1430, 1400, 1100 cm^{-1}; δ_H (500 MHz, DMSO-d_6): 7.84 (2H, m), 7.95 (2H, m,), 8.70-8.74 (1H, m), 8.86-8.92 (1H, m), 8.91 (1H, ddd, *J* 8.3, 7.7, 1.0 Hz, H6), 9.92 (1H, dd, *J* 6.5, 1.0 Hz, H8), 9.95 (s, 1H, H2); δ_C (125 MHz, DMSO-d_6): 128.8, 129.9 (2C), 131.5, 132.0, 132.8 (2C), 135.7, 138.5, 142.1, 144.8, 149.0, 168.4.

*2-Methyl-4-phenylpyrido[2,1-f][1,2,4]triazinium perchlorate (**4c**)*

This compound was prepared using Method B to give 0.1 g (31%), mp 269-271 °C (nitromethane-ethanol, white plates); [Found: C, 52.51; H, 3.94; N, 12.88. $C_{14}H_{12}ClN_3O_4$ requires C, 52.27; H, 3.76; N, 13.06%]; IR (KBr): 3050, 2930, 1570, 1510, 1460, 1405, 1100 cm^{-1}; UV (EtOH): 296 (4.09), 232 (4.23), shoulder: 350, 325 nm; δ_H (500 MHz, DMSO-d_6): 2.96 (3H, s, CH_3), 7.75 (1H, m), 7.83 (2H, m), 7.92 (2H, m), 8.64 (1H, t, *J* 7.8 Hz), 8.79-8.85 (2H, m,), 9.81 (1H, d, *J* 5.2 Hz, H8); δ_C (125 MHz, DMSO-d_6): 23.4, 128.0, 129.2 (2C), 130.4 (2C), 130.8, 132.6, 132.7, 133.4, 141.0, 143.5, 164.3, 168.4. Starting from **3a** and using Method C, 1.26 g (39%) of product was prepared, mp 269-271 °C. The compound was identical with that obtained earlier.

*2,4-Diphenylpyrido[2,1-f][1,2,4]triazinium perchlorate (**4d**)*

Prepared using Method B; 0.16 g (41%), mp 265-267 °C (acetonitrile-water, white plates); [Found: C, 59.18; H, 3.87; N, 10.70. $C_{19}H_{14}ClN_3O_4$ requires C, 59.46; H, 3.68; N, 10.95%; IR (KBr): 3100, 3060, 1590, 1550, 1495, 1440, 1395, 1100 cm^{-1}; δ_H (500 MHz, DMSO-d_6): 7.72-7.89 (6H, m), 8.07 (2H, m), 8.59 (2H, m), 8.70 (1H, m), 8.87 (2H, m), 9.94 (2H, d, *J* 5.2 Hz); δ_C (125 MHz, DMSO-d_6): 128.7, 129.3 (2C), 129.8 (2C), 130.0 (2C), 131.1 (2C), 131.6, 132.3, 133.4, 133.5, 134.3, 134.4, 142.1, 144.0, 160.0, 169.5. Starting from **3a** and using Method C, 1.49 g (39%) of white crystals were prepared, mp 265-267 °C.

*2-t-Butyl-4-phenylpyrido[2,1-f][1,2,4]triazinium perchlorate (**4e**)*

This compound was prepared by Method C; 1.49 g (41%), mp 251-253 °C; [Found: C, 56.35; H, 5.20; N, 11.22. $C_{17}H_{18}ClN_3O_4$ requires C, 56.12; H, 4.99; N, 11.55%]; IR (KBr): 3090, 3050, 2970, 1575, 1560, 1480, 1440, 1090, 690 cm^{-1}; δ_H (500 MHz, DMSO-d_6): 1.53 (s, 9H), 7.74 (2H, m), 7.80 (1H, m), 7.94 (2H, m), 8.61 ((1H, t, *J 7.9* Hz), 8.78-8.84 (2H, m), 9.80 (1H, d, *J* 5.0 Hz); δ_C (125 MHz, DMSO-d_6): 28.4 (3C), 110.0, 128.3, 129.7 (2C), 131.0 (2C), 131.1, 133.1, 133.5, 133.8, 142.0, 144.1, 168.6, 172.4.

Phenyl-2-pyridyl (*N*-acyl)ketimine (**6c**-**e**).

General method: A solution of the appropriate acid chloride (0.11 mol) in dry toluene (30 mL) was dropped into a stirred solution of **5** (20 g, 0.11 mol) and triethylamine (11.1 g, 15.3 mL, 0.11 mol) in dry toluene (70 mL) at 0 °C. The reaction mixture was stirred for 1 h, filtered and the solvent was evaporated. The residue was recrystallized to give the product.

Phenyl-2-pyridyl (N-acetyl)ketimine (***6c***)

This compound was prepared by the general procedure using acetyl chloride as reagent to give 14.9 g (66.5%) of white crystals, mp 83-85 °C (diethyl ether); [Found: C, 75.24; H, 5.53; N, 12.60. $C_{14}H_{12}N_2O$ requires C, 74.98; H, 5.39; N, 12.49%]; IR (KBr): 3010, 2880, 1670, 1640, 1580, 1500, 1440 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.12 (3H, s, C<u>H</u>$_3$-*N*-acetyl), 7.51-7.55 (3H, m, H-phenyl), 7.70-7.85 (4H, m H-4, H-5-pyridyl, H-phenyl), 7.93 (1H, dd, *J* 6.5, 2.0 Hz, H3-pyridyl), 8.69 (1H, dd, *J* 6.8, 1.7 Hz, H6-pyridyl).

*Phenyl-2-pyridyl (N-benzoyl)ketimine (**6d**)*

This compound was prepared by the general procedure using benzoyl chloride as reagent to give 25.7 g (90%) of white crystals, mp 104-106 °C (diethyl ether / CH_2Cl_2 = 2 : 1)); [Found: C, 79.92; H, 5.10; N, 9.67. $C_{19}H_{14}N_2O$ requires C, 79.90; H, 4.93; N, 9.78C%]; IR (KBr): 3050, 3000, 1655, 1625, 1600, 1570, 1440, 690 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.51-7.55 (3H, m, H-phenyl), 7.60-7.85 (7H, m, H-phenyl, H-benzoyl), 7.74-7.79 (2H, m H-4, H-5-pyridyl), 7.90 (1H, dd, *J* 6.5, 2.0 Hz, H3-pyridyl), 8.73 (1H, dd, *J* 6.9, 1.6 Hz, H6-pyridyl).

*Phenyl-2-pyridyl (N-pivaloyl)ketimine (**6e**)*

This compound was prepared by the general procedure using pivaloyl chloride as reagent to give 23.1 g (79%) of white crystals, mp 85-87 °C (petroleum ether)); [Found: C, 76.91; H, 6.98; N, 10.44. $C_{17}H_{18}N_2O$ requires C, 76.66; H, 6.81; N, 10.52 %];. IR (KBr): 3070, 3050, 2910, 1660, 1625, 1570, 1470, 1440, 690 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.25 (9H, s, C<u>H</u>$_3$-N-*t*Bu), 7.49-7.52 (3H, m, H-phenyl), 7.75-7.83 (4H, m H-4, H-5-pyridyl, H-phenyl), 7.98 (1H, dd, *J* 6.8, 1.9 Hz, H3-pyridyl), 8.70 (1H, dd, *J* 7.0, 1.8 Hz, H6-pyridyl).

*2-Chloro-4-phenylpyrido[2,1-f][1,2,4]triazinium perchlorate (**8**)*

A suspension of **3a** (0.37 g, 1 mmol) and urethane (0.18, 2 mmol) in $POCl_3$ (5 mL) was refluxed for 1 h. The excess of

$POCl_3$ was evaporated *in vacuo*, the residue was mixed with acetic acid (3 mL) and 70% $HClO_4$ (0.1 mL) and diethyl ether (3 mL). The precipitate was filtered off, washed with diethyl ether to give 0.3 g (88%) of beige crystals, mp 274-277 ^oC;[Found: C, 45.93; H, 2.45; N, 11.98. $C_{13}H_9Cl_2N_3O_4$ requires C, 45.64; H, 2.65; N, 12.28%]; IR (KBr): 3080, 1605, 1600, 1550, 1500, 1450, 1100 cm^{-1}; δ_H (500 MHz, DMSO-d_6): 7.79 (2H, m, H3' + H5'); 7.89 (1H, m, H4'); 7.96 (2H, m, H2' + H6'); 8.76 (1H, td, *J* 6.5, 3.2 Hz, H7); 8.94 (2H, m, H5 + H6); 9.95 (1H, d, *J* 6.5 Hz, H8); δ_C (125 MHz, DMSO-d_6): 129.0 (C5), 129.4 (C3' + C5'), 130.1 (C7), 130.9 (C2' + C6'), 131.7 (C1'), 131.8 (C4'), 133.7 (C4a), 141.5 (C8), 144.8 (C6), 159.3 (C2), 171.6 (C4).

*2-Morpholino-4-phenylpyrido[2,1-f][1,2,4]triazinium perchlorate (**9a**)*

A mixture of **8** (0.34 g, 1 mmol) and morpholine (0.17 g, 2 mmol) in acetonitrile (5 mL) was refluxed for 1 h. The reaction mixture was cooled down to rt, and ethyl acetate (3 mL) was added. The precipitate was filtered off, washed with diethyl ether to give 0.30 g (76%) of yellow crystals, mp 176 ^oC.;[Found: C, 51.72; H, 4.40; N, 14.32. $C_{17}H_{17}ClN_4O_5$ requires C, 51.98; H, 4.36; N, 14.26%]; δ_H (500 MHz, DMSO-d_6) : 3.80 (4H, t, *J* 4.6 Hz, N-CH_2), 3.96 (4H, br. s, O-CH_2), 7.72 (2H, m, H3' + H5'), 7.78, (1H, m, H4'), 7.88 (2H, m, H2' + H6'), 8.34 (1H, ddd, *J* 7.2, 6.4, 1.7 Hz, H7), 8.37 (1H, ddd, *J* 8.2, 7.2, 1.3 Hz, H6), 8.45 (1H, dd, *J* 8.2, 1.7 Hz, H5), 9.32 (1H, dd, *J* 6.4, 1.3 Hz, H8); δ_C (125 MHz, DMSO-d_6): 44.2 (N-CH_2), 66.0 (O-CH_2), 127.9 (C5), 129.0 (C3' + C5'), 130.1 (C2' + C6'), 130.5 (C7), 131.3 (C4a), 132.4 (C4'), 132.9 (C1'), 137.9 (C8), 138.8 (C6), 156.7 (C2), 168.0 (C4).

*2-Diethylamino-4-phenylpyrido[2,1-f][1,2,4]triazinium perchlorate (**9b**)*

A mixture of **8** (0.34 g, 1 mmol) and diethylamine (0.15 g, 2 mmol) in acetonitrile (5 mL) was refluxed for 1 h. The reaction mixture was cooled down to rt, and ethyl acetate (3 mL) was added. The precipitate was filtered off, washed with diethyl ether to give 0.28 g (74%) of yellow crystals, mp 164-165 ^oC.;[Found: C, 53.78; H, 5,01; N, 14.81. $C_{17}H_{19}ClN_4O_4$ requires C, 53.90; H, 5.06; N, 14.79%]; δ_H (500 MHz, DMSO-d_6) (ppm): 1.25 (3H, t, *J* 6.4 Hz, N-CH_2-C$\underline{H}_3$), 1.32 (3H, t, *J* 6.4 Hz, N-CH_2-C$\underline{H}_3$), 3.75 (2H, q, *J* 6.4 Hz, N-C$\underline{H}_2$-CH_3), 3.82 (2H, q, *J* 6.4Hz, N-C$\underline{H}_2$-CH_3), 7.71 (2H, m, H3' + H5'), 7.78 (1H, m, H4'), 7.86 (2H, m, H2' + H6'), 8.29 (1H, ddd, *J* 7.3, 5.9, 1.6 Hz, H7), 8.31 (1H, ddd, *J* 8.2, 7.3, 1.2 Hz, H6), 8.39 (1H, dd, *J* 8.2, 1.6 Hz, H5), 9.29 (1H, dd, *J* 5.9, 1.2 Hz, H8); δ_C (125 MHz, DMSO-d_6): 11.8 + 13.4 (N-CH_2-$\underline{C}H_3$), 42.4 (N-$\underline{C}H_2$-CH_3), 127.7 (C5), 129.0 (C3' + C5'), 129.9 (C2' + C6'), 130.2 (C7), 131.2 (C4a), 132.1 (C4'), 133.2 (C1'), 137.1 (C8), 138.6 (C6), 156.4 (C2), 167.6 (C4).

*N-(Pyridin-2-ylmethyl)formamide (**11a**)*

A solution of pyridin-2-ylmethanamine (**10a**, 10.8 g, 10.3 mmol) and ethyl formate was heated under reflux with magnetic stirring for 1.5 h. After completion of the reaction, the resulting mixture was evaporated to give the final product **14** as yellow oil, 13.5 g (quant.)[14].

N-(phenyl(pyridin-2-yl)methyl)formamide (***11b***)

To phenyl(pyridin-2-yl)methanamine hydrochloride (**10b**, 1.167 g, 5.28 mmol) an aqueous solution of sodium hydroxide (0.217 g, 5.42 mmol in 2 mL) was added, and the mixture was stirred at room temperature for 30 min. Then it was extracted with dichloromethane (3 x 2mL). The organic phase was dried over Na_2SO_4, filtered and evaporated to yield the product as yellow oil (1.117 g, quant.); IR(KBr): 3279, 2856, 1671, 1495, 699, cm^{-1}; δ_H (300 MHz, $CDCl_3$): 6.23 (1H, d, *J* 7.2 Hz, H1), 7.18-7.35 (7H, m, H3′, H5', H2″, H3″, H4″, H5″, H6″), 7.60-7.66 (1H, m, H4'), 7.80 (1H, br. s, NH), 8.32 (1H, s, H-C=O), 8.56 (1H, d, *J* 4.8 Hz, H6'); δ_C (75 MHz, $CDCl_3$): 56.0 (C-1), 122.6 (C-4″), 122.8 (C-5′), 127.3 (C-2″, C-6″), 127.6 (C-3′), 128.7 (C-3″, C-5″), 137.0 (C-4′), 141.4 (C-1″), 148.8 (C-6″), 158.2 (C-2′), 160.2 (C=O). HRMS (ES) for $C_{13}H_{12}N_2O$ $[M+H]^+$: calcd 212.2474, found 212.2463.

*3,4-Dihydropyrido[2,1-f][1,2,4]triazinium perchlorate (**13a**)*

To the solution of 1-amino-2-(ammoniomethyl)pyridin-1-ium perchlorate and tosylate (**14**, 2.00 g, 5 mmol) and acetonitrile (2.5 mL), triethyl ortoformate (0.69 mL, 0.5 g, 3.3 mmol) was added and refluxed under magnetic stirring for 3 h. After completion of the reaction (monitored by TLC), the mixture was evaporated in order to reduce its volume to 3 mL. $HClO_4$ (70%, 0.5 mL) and hot ethyl acetate (15 mL) was added to the solution, then cooled to give colorless crystals. The product was collected by filtration (1.0 g, 85%, mp 194-199 °C; [Found: C, 35.69; H, 3.60; N, 18.20. $C_7H_8ClN_3O_4$ requires C, 35.99; H, 3.45; N, 17.99%]; IR (KBr): 3338, 3043, 1640, 1334, 1087 cm^{-1}; δ_H (300 MHz, DMSO-d_6): 4.87 (2H, s, C(4)H_2), 7.75-7.78 (2H, m, H2, H5), 7.87 (1H, m, H7), 8.30-8.36 (1H, dt, *J* 7.8, 1.2 Hz, H6), 8.67 (1H, d, *J* 6.3 Hz, H8), 8.83 (1H, br. s, NH); δ_C (75 MHz, DMSO-d_6): 37.9 (C4), 126.3 (C5), 126.8 (C7), 140.1 (C4a), 140.5 (C8), 143.1 (C6), 150.4 (C2).

*4-Phenyl-3,4-dihydropyrido[2,1-f][1,2,4]triazinium perchlorate (**13b**)*

To the solution of *N*-(phenyl(pyridin-2-yl)methyl)formamide (**11b**, 0.25 g, 1.1 mmol) in dichloromethane (2 mL) was cooled down to 0 °C solution of TSH (0.21 g) in dichloromethane (6 mL) was added under magnetic stirring at 0 °C for 30 min. The reaction mixture was allowed to warm up to rt and maintained at this temperature for 3 h. $HClO_4$ (70%, 1 mL) was added to the mixture, stirred for further 3 h. After completion of the reaction (2 d, without magnetic stirring), the precipitated product was filtered off as white crystals (0.33 g, 79%, mp 116-120 °C; IR (KBr): 3387, 1633, 1490, 1085, 625 cm^{-1}; δ_H (300 MHz, DMSO - d_6): 6.28 (1H, br. s, H4), 7.39-7.46 (5H, m, H2′, H3′, H4′, H5′, H6'), 7.73 (1H, d, *J* 7.8 Hz, H5), 7.89 (1H, m, H7), 8.01 (1H, d, *J* 4.8 Hz, H2), 8.29 (1H, m, H6), 8.78 (1H, d, *J* 6.6 Hz, H8), 9.70 (1H, br. s, NH); δ_C (75 MHz, DMSO-d_6): 51.1 (C4), 127.1 (C7), 127.2 (C5), 127.3 (C2′, C6′), 129.5 (C3′, C4′, C5′), 140.7 (C8), 140.9 (C4a), 141.9 (C1′), 143.5 (C6), 149.2 (C2).

*1-Amino-2-(ammoniomethyl)pyridinium tosylate perchlorate (**14**)*

The mixture of *N*-(pyridin-2-ylmethyl)formamide (**11a**, 1.40 g, 10.28 mmol) and dichloromethane (10 mL) was cooled down at 0 °C in a round-bottomed flask, then the solution of TSH (0.73 g) in dichloromethane (30 mL) was added under magnetic stirring at 0 °C for 30 min. The reaction mixture was allowed to warm up to rt and maintained at this temperature for 3 h. $HClO_4$ (70%, 1 mL) was added to the mixture, stirred for further 3 h. After completion of the reaction (2 d, without magnetic stirring), the mixture was concentrated under reduced pressure. The residue was diluted with acetonitrile (20 mL) and water (1 mL) and heated. Hot ethyl acetate (10 mL) was added dropwise to the solution, then it was cooled down, whereupon a solid product

deposited. The product was collected by filtration as colorless crystals (2.76 g, 68%, mp 192-195 °C); [Found: C, 39.12; H, 4.74; N, 10.37. $C_{13}H_{18}ClN_3O_7S$ requires C, 39.45; H, 4.58; N, 10.62%]; IR (KBr): 3307, 2930, 1505, 1209, 1084 cm^{-1}; δ_H (300 MHz, DMSO-d_6): 2.28 (3H, s, CH_3), 4.53 (2H, m, CH_2), 7.12 (2H, m, H3′, H5′), 7.45 (2H, m, H2′, H6′), 8.04-8.08 (7H, m, H3, H5, NH_2, $^+NH_3$), 8.47 (1H, m, H4), 8.95 (1H, d, *J* 6.0 Hz, H6); δ_C (75 MHz, DMSO-d_6): 20.8 (CH_3), 38.2 (CH_2), 125.4 (C2′, C6′), 127.8 (C3, C5), 128.2 (C3′, C5′), 137.9 (C4′), 141.8 (C6), 142.4 (C4), 145.1 (C1′), 146.6 (C2).

*1-Amino-2-(4-chlorobenzoyl)-4,6-dimethylpyrimidinium tosylate **(16)***

A freshly prepared solution of TSH (1.14 g, 6.1 mmol) in dichloromethane (50 mL) was added to a stirred solution of (4-chlorophenyl)(4,6-dimethylpyrimidin-2-yl)methanone (**15**)[15] (1.5 g, 6.1 mmol) in dichloromethane (20 mL) at 0 °C. The reaction mixture was stirred for 30 min, then it was allowed to warm up to rt. After completion of the rection (3 h), diethyl ether was added to the solution, the precipitated crystals were filtered off and recrystallized from acetonitrile to give the product as white-yellow crystals (1.27 g, 48%, mp 174-176 °C); [Found: C, 55.10; H, 4.41; N, 9.35; S, 7.67. $C_{20}H_{20}ClN_3O_4S$ requires C, 55.36; H, 4.65; N, 9.68; S, 7.38%]; IR (KBr): 3218, 3100, 1689, 1221, 1010 cm^{-1}; δ_H (300 MHz, DMSO-d_6): 2.29 (1H, s, CH_3 (TsO)), 2.74 (3H, s, 4-CH_3), 2.85 (3H, s, 6-CH_3), 7.11 (2H, m, H-3″, H-5″), 7.23 (1H. br. s, NH_2), 7.46 (2H, m, H-2″, H-6″), 7.68 (2H, m, H-3′, H-5′), 7.99 (2H, m, H-2′, H-6′), 8.28 (1H, br. s, H-5); δ_C (75 MHz, DMSO-d_6): 18.5 (CH_3-(TsO)), 20.8 (6-CH_3), 24.4 (4-CH_3), 124.9 (C-5), 125.5 (C-2″, C-6″), 128.0 (C-3″, C-5″), 129.6 (C-3′, C-5′), 131.5 (C-4′), 137.7 (C-2′, C-6′), 137.7 (C-4″), 140.9 (C-1′), 145.5 (C-1″), 156.9 (C-2), 166.4 (C-4, C-6), 174.4 (C=O).

4-(4-Chlorophenyl)-6,8-dimethylpyrimido[2,1-*f*][1,2,4]triazinium perchlorate ***(17)***

Method A: $POCl_3$ (15 mL) was dropped into a stirred solution of **7** (5 g, 11.5 mmol) in formamide (25 mL) at 80 °C **(Caution: HCN was liberated throughout the process!)**. Stirring was continued at 80 °C for 1 h and poured on ice-water. The solution was mixed with 70% $HClO_4$ (0.5 mL) and extracted with nitromethane (3 x 15 mL). Charcoal was added to the organic extract and it was dried over $MgSO_4$, filtered and the solvent was evaporated. The residue was recrystallized from acetonitrile-ethyl acetate to give pale yellow crystals (0.7 g, 16%, mp 172-174 °C; [Found: C, 45.52; H, 3.54; N, 14.88. $C_{14}H_{12}Cl_2N_4O_4$ requires C, 45.30; H, 3.26; N, 15.09%]; IR (KBr, cm^{-1}): 3420, 3073, 1630, 1478, 1095; δ_H (300 MHz, CD_3CN): 2.97 (3H, s, 6-CH_3), 3.07 (3H, s, 8-CH_3), 7.69 (2H, m, H3′, H5′), 8.34 (1H, s, H7), 8.44 (2H, m, H2′, H6′), 9.67 (1H, s, H2); δ_H (75 MHz, CD_3CN): 19.4 (8-CH_3), 26.0 (6-CH_3), 127.7 (C7), 130.0 (C3′, C5′), 131.7 (C4′), 134.2 (C2), 134.9 (C2′, C6′), 141.3 (C1′), 160.0 (C6, C8), 167.5 (C4a), 176.2 (C4).

Method D: $TiCl_4$ (3.8 g, 2.2 mL, 20 mmol) was dropped into dioxane (10 mL) under stirring at 25 ±10 °C. *N*-aminopyrimidinium salt **16** (5 mmol) was added to the yellow suspension and it was heated up to 95 °C. Formamide (3 mL) was added to the reaction mixture and it was refluxed for 30 min. Water (30 mL) and 70% $HClO_4$ (5 mL) were added to the cooled reaction mixture and the resulting solution was extracted with nitromethane (3 x 30 mL). The combined organic extract was evaporated to dryness, the residue was recrystallized from a mixture of acetonitrile-ethyl acetate to give pale yellow crystals (0.96 g (52%).

The compound was identical with that obtained by **method A**.

Dedication

This paper is cordially dedicated to Professor Leon Ghosez for acknowledgment of his long lasting successful and high level activity at Tetrahedron.

Appendix A. Supplementary data

Supplementary data to this article can be found online at

https://doi.org/

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